UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Doherty

DATE: July 18, 1978

001435

(6)

SUBJECT: Tolerances for permethrin:
on cottonseed at 0.5 ppm
in meat, fat, and byproducts at 0.05 ppm
(including cattle, horses, hogs, sheep, goats, poultry, milk and eggs)
#8F2044 Registration #10182-18 Caswell [redacted]

FROM: Martha Panitch, Ph.D.
Toxicology Branch, HED (TS-769)

Martha Panitch Ph.D.
September 13, 1978

TO: Mr. Charles Mitchell
Registration Division (TS-767)

Petitioner: ICI-Americas, Inc.
Wilmington, Delaware

Residue chemistry considerations: Memo of April 24, 1978 confirmed the above tolerances The residues on cottonseed are expected to be real. Some transfer to animals from feed has also been documented. However, cottonseed byproducts apparently do not contain residues.

Recommendations:

1. TOX Branch can not complete the hazard evaluation before the remaining issues raised by the two cross referenced oncogenicity studies are resolved, see memo of conference Feb. 24, 1978 and review conclusions memo of March 30, 1978.

2. See further comments at the end of the review.

Review: The following studies have been reviewed as noted:

See Studies on Next Page.

SGR = 10

Rat wt = 14

Mouse Book = 24

1 of 27

Review: The following studies have been reviewed as noted:

Species	Study	Memo date	Status	NEL	Other tested doses
RAT:	28day feeding	this review	Suppl	?	200, 500, 1000, 2500, 5000, 10,000 ppm
	28day/reversal	this review	OK	(<2500ppm)	2500 ppm
	90day feeding	5/10/76	OK	20 ppm	100 500 2500ppm
?	180day feeding	3/4/77 ?	Suppl	?	375 750 1500 3000 ppm
	180day/special	this review	OK	20 ppm	100 1000 ppm
	teratology	5/10/76	OK	200 mg/kg	None
	pregnt rising dose	3/4/77	OK	150 mg/kg	100 225 338mg/kg
	teratology	3/4/77	OK	225 mg/kg	22.5 71mg/kg
	3-gen reprod	3/30/78	OK	100 ppm	20 ppm
	3-gen reprod	this review	OK		
	/reprod & Tertology effects		-	2500 ppm	500 1000 ppm
	/parent. & offspring effects		-	(<500 ppm)	
	2-yr feeding	3/30/78	OK	20 ppm	100 500 ppm
	/oncogenitity		Suppl	?	
	2-yr feeding	this review	OK	(<500 ppm)	500, 1000, 2500ppm
	/ oncogenicity		OK		
MOUSE:	dominant lethal /(mutagenicity)	3/4/77	OK	150 mg/kg	15, 48 mg/kg
	teratology	5/10/76	OK	400 mg/kg	None
	2-yr feeding	3/30/78	Suppl	20 ppm	500, 4000 ppm
	/oncogenicity	"	Suppl	?	
	98 wk feeding	this review	Suppl	(<250 ppm)	200, 1000/2500
	/oncogenicity		OK	No suggestion of effect	

Species	Study	Memo date	Status	NEL	Other tested doses
RABBIT:	teratology	5/10/76	OK	400 mg/kg	None
DOG:	90-day oral	5/10/76	OK	5 mg/kg	50, 500 mg/kg
	90-day oral	3/4/77	Suppl	?	10, 100, 2000mg/kg

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Referenced Petitions:

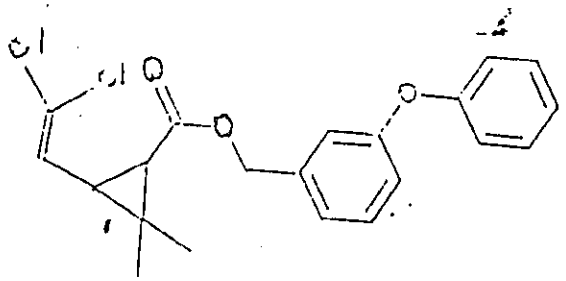
ICI and FMC have agreed to share the permethrin data which resides in petitions 6G1769, 7G1891, 7G1901, 7G1917, 8G2029, 8F2034 and 8F2044.

Pertinent memos:		
	May 10, 1976	6G1769
	March 4, 1977	7G1891
	March 15, 1977	6G1769
	April 3, 1977	7G1901
	May 7, 1977	6G1769 & 7G1891
	Jan. 12, 1978	8G2029 & 8F2034
	March 30, 1978	8F2034

Chemical Name: m-phenoxybenzyl-cis-(trans)-3-(2,2-dichlorovinyl)-2, 2-dimethylcyclopropone carboxylate

Synonyms: Technical material has been identified under codes P557, R86557, FMC 33297, NRDC 143. Formulated materials have been designated Ectiban, Matadan 3.2 ED, FMC 35171 1.6 EC, SBP-1513 EC-1, JFU 5054, and JFU 5055. These varied between 13.3% and 28.2% active ingredient. Ambush (ICI) and Pounce (FMC) are proposed trade names.

Structure:



Rat: Acute Toxicity in Males - Technical CTL/P/388 conducted in November 1977.

The rats used weighed 150-230 gr and were SPF-Wistar derived animals bred at Alderley Park. The study was submitted by ICI-Americas, Inc., Wilmington, Delaware, Jan. 27, 1978.

Oral: Permethrin was given by gavage to 6 fasted rats for each dose of 1600, 2000, 2500, 3200, and 4000 mg/kg. Observations continued for 14 days.

Results: The LD_{50} was calculated to be 2949 mg/kg.

Toxicity: All rats given 4000 mg/kg died, while all given 2000 mg/kg or less survived. All deaths occurred in 2 hr. Survivors showed tremors, nervous hyperactivity, urinary incontinence, and salivation. A few were subdued, comatose, ataxic, or showed piloerection, lacrimation, or fecal incontinence. Only 1 of 6 rats showed any effect at 1600 mg/kg.

Classification: Minimum Data

Toxicity Category: III - Caution

Dermal: Permethrin was melted and applied to the shorn backs of 6 rats at the rate of 4 ml = 5176 mg /kg. This was covered with aluminum foil for 24 hr and then washed off. Observations continued for 2 weeks.

Results: No lethality was observed. LD_{50} >5176 mg/kg.

Toxicity: All rats showed tremors or hyperactivity.

Classification: Minimum Data

Comment: Although application of a melted material is unusual, sufficient absorbtion apparently took place to cause observable effects similar to those seen after oral treatment. (Meeting 7/12/78 with ICI--material is liquid at body temperature.)

Toxicity Category: III - Caution

Acute Studies of Formulated Material - Report CTL/P/384 conducted between June and October 1977.

The formulation tested is identified as JFU 5054; an emulsifiable concentrate. It is 24% (w/v) permethrin.

Oral/Rats: of Alderley Park strain were used. Five male and five female were given each dose of 2.1, 4.2, 6.7, 8.4 10.4 and 13.3 ml of JFU 5054 per kg by gavage. Observation continued for 14 days.

Results: The LD_{50}'s (with 95% confidence limits) were:

	ml JFU 5054/kg	mg permethrin/kg
males	12.8 (8.4-19.5)	3070 (2020-4070)
females	9.6 (7.1-12.9)	2305 (1715-3100)

Toxicity: Signs observed between 6 hr and 7 days included subdued behavior, tremors, ataxia, urinary incontinence, salivation and pilo-erection. Most deaths occurred between 1 and 2 days.

Classification: Minimum-Data

Toxicity Category: III - Caution

Dermal Toxicity/Rabbits: A dose of 2 ml undiluted JFU 5054 per kg was applied to the shaven backs of 4 males and 4 females. Two of each sex had abrasions. The material was covered with aluminum foil for 24 hrs. and then washed off. Observations continued for 2 weeks.

Results: No lethality was observed, so the LD_{50} must be greater than 2 ml JFU 5054, or 480 mg permethrin, per kg.

Toxicity: No effects were observed in any of the 8 rabbits.

Classification: Core/Guidelines

Toxicity Category: III - Caution - on the formulated material

Skin Irritation/Rabbits: A dose of 0.25 ml undiluted JFU 5054 was applied to each 25 mm square test area of intact and abraded skin of 6 female rabbits. The material was covered with aluminum foil for 24 hr. the area was then washed and scored by the Draize method immediately and after an additional 48 hr.

Results: Both edema and erythema, slight to mild, were observed at all application sites at both observation periods. The primary irritation index = 3.37.

Classification: Core/Guidelines

Toxicity Category: IV - (No precautionary statement.)

Eye Irritation/Rabbits: A dose of 0.1 ml was placed in the conjunctival sac of one eye of each of 9 female rabbits. For 3 animals this was washed out after 4 sec.

Results: There was an initial pain reaction. Conjunctival irritation was rated 8 (of 20) in unwashed eyes and 7 in washed eyes at 2 hr. These scores decreased to 1 by day 3 in both groups, and had vanished by day 7. Iris irritation was seen only at score 2 (of 10) only at 2 hr in unwashed eyes. No corneal effects were found.

Classification: Minimum Data

Toxicity Category: III - Caution

Acute Inhalation/Rat: (CTL/P/386) or (CTL/P/383) probably conducted between October 24 & Dec. 1, 1977.

The formulation is identified by the synonyms "AMBUSH" 2.E. or JFU 5054. This contained 24% (w/v) permethrin.

Four male and four female SPF-Alderley Park albino rats were exposed to vapors at 0.83 mg/l atmospheric concentration flowing at 4 l/min, for 4 hr. The rats were returned to their cages and observed for 14 days.

Results: No lethality was observed so the LD_{50} must be above 0.83 mg/l.

Clinical Observations: During exposure the following sequence of changes was observed. At 35 min, snouts began to redden. At 1 hr a nasal discharge was noted. By 2 hr there were reduced responses to stimuli. The animals proceeded to appear moribund with severe nasal discharge, and piloerection.

Following termination of exposure, only 1 1/2 hr was necessary to reverse all signs of toxicity.

These signs do not resemble those of permethrin technical.

Body weights: Rate of gain matched controls.

Necropsy: No abnormalities of major organs were found.

Classification: Minimum Data

Toxicity Category: II - Warning

Rat: 28-Day Feeding Study

The rats used were SPF-Wistar derived animals 4-5 weeks old from the Alderley Park colony. The Central Toxicology Labs of ICI-Ltd., England, conducted the study beginning in June 1975. It was submitted by ICI--Americas, Inc., Wilmington, Delaware on January 27, 1978, as Report #CTL/P/355.

The doses of permethrin studied were 200, 500, 1000, 2500, 5000, and 10,000 ppm. The permethrin was mixed with corn oil for incorporation into the diet, which was then pelleted. Controls received an equivalent corn oil contain diet. Eight rats per sex per dose were observed for symptoms, growth and food consumption. Only 4 per sex per dose were studied for clinical laboratory measures, organ weights or histopathology.

Results: Piloerection, whole body tremors, and hyperactivity preceeded death among rats fed 10,000 ppm. These symptoms were seen without necessarily leading to death among rats fed 5000, 2500, or 1000 ppm. The incidence, severity, and duration of these symptoms were clearly dose dependant. One additional sign occurred in rats fed 5000 ppm--urinary incontinence. The dietary concentration which caused these symptoms initially yielded doses of 150 to 550 mg/kg/day.

Rats fed 500 ppm (initially 35 mg/kg/day) and 200 ppm showed no differences from control.

Mortality: Six males and 3 females fed 10,000 ppm died the first day. The rest of that group died by the third day. Three males and 1 female fed 5000 ppm died days 3 and 4. Another male of this group died day 18.

Body weight: Rats fed 5000 ppm showed a severe suppression of weight gain during the first week. This effect gradually diminished, so that the rate at which weight was gained almost matched control by the fourth week. For females, body weight had almost caught up. Rats fed 2500 ppm showed no suppression of weight gain. In fact, females averaged 5 to 8% heavier than controls during weeks 2, 3 and 4. Animals fed 1000 ppm or less showed no differences from control.

Food Consumption: Differences were found which paralleled the body weight differences.

Water Consumption: No differences between groups were found.

Hematology: Samples were taken prior to dosing, and at 4 weeks. RBC, HCT, and HGB showed no differences. WBC became elevated in males fed 2500 or 5000 ppm. This was a lymphocytosis. Neutrophils, monocytes, eosinophils and platelets showed no differences. Females showed no intergroup differences.

Coagulation: Prothrombin time and activated parcial thromboplastin time were not altered by permethrin treatment.

Bone Marrow: Smears showed no abnormalities.

Blood Chemistries: Mean values for SGOT and SGPT from control males and females showed little change from pretreatment to 4 weeks. Means from treated groups were all lower, except the lowest dose males, although the differences did not reach statistical significances, and then was no dose dependancy.

No differences were found in blood glucose or urea.

Urinalysis: Pooled samples collected prior to treatment and after 4 weeks were analysed for volume, pH, specific gravity, protein, glucose, and bilirubin. No biologically important differences were found.

Organ weights: Mean liver weights were increased 12 and 14% among males fed 2500 and 5000 ppm. At the same doses, female liver weights were increased 30 and 33%. Organ to body weight ratios were more clearly dose dependant. At 5000 ppm the ratios were increased 40-50% compared to control. Those fed 2500 showed 17 to 19% increases. Statistically significant increases of 8% were also seen among females fed 1000 or 200 ppm, but a like decrease was recorded for those fed 500 ppm.

Kidney, adrenal, gonads, lungs, heart, brain, pituitary and thymus showed no pattern of changes suggestive of chemical induction.

Gross pathology: Among animals which died, 7 of the males had hemorrhages in brain. Five of these were fed 10,000 and 2 were fed 5000. Hemorrhages were also found twice in lung, and in adrenals and intestines each in one animal. Other findings in lungs of males fed 10,000 ppm were each seen in two animals. These included lack of deflation, dark patches, and edema. The females which died showed none of these changes. No two of them showed any other abnormalitiy, although enlarged lymph nodes were noted in one female and one male.

Few abnormalities were found among the rats sacrificed at 4 weeks. One male fed 5000 ppm had a hemorrhage on the skull. One female fed 5000 ppm had an enlarged lymph node. No other finding resembling those in the animals which died were found in animals which were sacrificed.

Two of the 4 males fed 500 ppm had proteinaceous material in the bladder at sacrifice. NOTE: While the other 4 per sex per group were scheduled for autopsy, no such reports were provided.

Histopathology: One male fed 5000 ppm had vacuolated cerebellar fiber tracts, while another showed increased vacuolization of the cortical cells. This may or may not have been due to a processing artifact.

No other abnormalities occurred that were not seen also among controls.

NOTE: No tissues were examined from animals which died, nor from those fed 200 ppm. The number of 4 per sex per dose was further reduced by machine failure. All tissues were lost from one control and one treated male. Brains were lost from another control and another treated male. The enlarged lymph node noted grossly was also lost.

Category: Supplementary. The limitations on the usefullness of this study derive from the limited number of animals subjected to each of the examinations, the short feeding period, the limited range of laboratory determinations, and the absence of individual data.

Conclusions: Doses approaching 5000 ppm or 550 mg/kg/day represent a maximally tolerated dose. At this dose 25% of the rats died in 4 days. At twice this dose all animals died, while half this dose killed none.

An NEL is difficult to identify from this study, at least partly because of the small number of animals examined.

Liver enlargement, calculated on a body weight basis, showed an approximately linear dose dependance among females fed 1000 ppm or more and among males fed 2500 ppm or more. However, females fed 200 ppm showed a statistically significant increase equal to that found at 1000 ppm. The intermediate dose of 500 ppm appeared to produce a decrease of about the same magnitude.

Tremors, piloerection, and hyperactivity also showed a dose dependant incidence, severity, and duration in animals fed 1000 ppm or more

An additional possible effect seen at 2500 ppm and higher was lymphocytosis.

Other effects seen at the maximally tolerated dose were urinary incontinence, and suppression of food consumption and body weight gain.

Rat: 3-Generation Reproduction

The rats used were weanling SPF-Wistar derived animals from the Alderley Park Strain. The Central Toxicology Labs of ICI, Ltd., England conducted the study beginning November 1975. The study was identified as No. CTL/P/361, and submitted by ICI-Americas, Inc., Wilmington, Delaware on Jan. 27, 1978.

The permethrin was administered in the diet at concentrations of 500, 1000 and 2500 ppm. The compound was mixed with corn oil for addition to the diet which was pelleted. The controls received the corn oil diet.

Each group in the F_0 generation contained 12 males and 24 females. Those numbers of parents were also selected from the F_1 and F_2 generations.

Each parent group was treated from weaning for 12 weeks and then mated. In each generation, the first litter was grossly autopsied at weaning. The parents were allowed to rest. Mating with different partners resulted in a second litter. Parents selected from the F_1 and F_2 generations were derived from the second litter. The remaining weanlings were grossly autopsied. The second litter of F_3 animals was partially examined histologically. A third F_3 litter was produced and examined for teratologic effects.

Clinical Observations: Whole body tremors occurred shortly after beginning feeding of 2500 in all parent generations except F_0 males. Actual intakes during these tremors ranged from 540 to 710 mg/kg/day. The F_0 males and F_1 males consumed nearly the same doses, 570 and 585 mg/kg/day respectively. The difference most likely arises from the nursing derived body burden in the F_1 males. Two each of the F_0 females fed 1000 ppm (210 mg/kg/day) and 500 ppm (110 mg/kg/day) also had tremors.

In addition, pregnant and lactating females fed 2500 ppm, in all generations showed tremors. These were more common in the second and third week of lactation. Two F_1 females fed 1000 ppm also had tremors in the third week of lactation. No control animals had tremors at any time. Other occurrences included conjunctivitis and ringtail showed no differences in incidence between treatment groups.

Mortalities: The following table shows the number of parent animals which were sacrificed due to illness. None were found dead.

ppm		C	500	1000	25000
Males	F_0	0	0	0	0
	F_1	0	1	1	0
	F_2	0	0	0	2
SUM			1	1	2
Females	F_0	0	1	2	0
	F_1	1	0	1	1
	F_2	0	0	0	4
SUM		1	1	3	5

Causes of death in females in 5 cases were related to difficulty in in littering and in another, no litter was observed. The other female showed hemorrhaging half way through gestation. Each of the males had a different illness.

Body weights: During the 12 week, post weaning, premating treatment period, parental body weights did not differ between treated and control groups. However, the F_1 and F_2 generations showed an early growth stimulant effect. In the F_1 generation, those fed 500 ppm showed the greatest growth. Males and females weighed up to 13.8 and 13.5% more than control. These peaks occurred at 3 and 2 weeks respectively. In the F_2 generation, those fed 1000 ppm showed the greatest growth, with the difference already clearly established at the end of weaning. At this time, the males were 13.6% heavier than control. The females reached their peak at week 1, at 12.3% above control.

These increased growth rates did not persist, except among the F_1 males. Both those fed 500 and those fed 1000 ppm had a total 12 week weight gain which was 7.5% greater than control. The growth rates were slowed in the other groups, so that the 12 week weight gain was like control. The F_2 males and females fed 2500 ppm showed sufficient slowing of growth rate by the end of 12 weeks to actually weigh less than control.

The stimulated growth effect was not uniform. For example, F_1 males fed 500 ppm showed 5-6 of the 12 animals which weighed more than the heaviest control. These weighed up to 50% more than the mean of C. These individuals also showed a sustained larger size. In contrast, the late suppression of the rate of weight gain at 2500 ppm in the F_2 generation appeared to be a small but uniform effect.

Weight gain during pregnancy also showed differences only in the F_1 and F_2 generation. The amount of weight gained was reduced among animals fed 500 or 1000 ppm. This was significant among F_1 females only during their second litter, but was seen during both litters among the F_2.

Food consumption and utilization: Those groups of animals with greater weight gain, tended to consume more food. The amount of food consumed for each gram of body weight gained was relatively constant.

Reproductive performance: No deleterious differences were found in the following measures which could be attributed to permethrin feeding; over all 6 litters:

Male fertility
Female fertility
Length of gestation
Viability
Sex ratio
Litter size
Lactation index

In contrast, there appeared to be slight enhancement by permethrin. Those fed 2500 ppm had a 6.1% higher over all pregnancy rate, and 6.6% greater mean litter size, yielding 13% more live young. The percentage born dead at this dose was only 2.5 compared to 4.1% among controls.

Parental Pathology: Gross examination of rats surviving the breeding program revealed no consequences of permethrin feeding.

Growth of offspring: Divergent effect on growth were recorded.

The weight gain was less only in the first litter of the F_2 generation. At 4 days, only the females fed 2500 had gained comparably to controls. By day 10, the males fed 1000 or 2500 ppm still showed growth suppresion. By day 21, all treated groups had caught up with controls.

Weight gain was greater than control among the second litter of the F_2 generation for those fed 1000 ppm. This difference appeared by day 4 and persisted through weaning in both sexes. Among those reserved for breeding, this difference persisted into the post weaning period. In addition, day 4 weights were higher than control among males fed 2500 ppm first litter F_1 generation; and the first litter of the F_3 generation fed 1000 ppm. Neither of these persisted to day 10.

Offspring clinical observation: Tremors were seen among those pups from mother fed 2500 ppm. These were observed at age 3-5 weeks among those "awaiting autopsy." It is not stated whether these were being fed compound, or may have been exhibiting withdrawal.

Ring tail, attributed to low humidity when seen among parents, was also seen on pups from both litters of the F_1 generation.

Offspring mortality: No differences in offspring death rate were found, which could be attributed to permethrin. However, there were higher death rates in all groups of the first F_1 litter. Toxic and infectio s causes were sought, but not found. However, noise and vibration from an adjacent building construction project was present during this litter, but not others.

Offspring pathology: Unilateral buphthalmos was induced by permethrin in 1 to 4 pups per litter as follows:

ppm	C	500	1000	2500
# of litters with affected pups	0	1	14	15
# of litters examined	12	120	130	131
Earliest litter with abnormality	-	2nd F_2	1st F_2	2nd F_1

Histopathology: The buphthalmos was due to persistent pupillary membranes.

Ten male and ten female weanlings from the second F_3 litter were examined. Livers showed permethrin-induced centrilobular hypertrophy and cytoplasmic eosinophilia. All dose groups were affected with dose dependant increases in both incidence and severity.

Cystitis and/or pylonephritis appeared to be increased at 2500. This was clearly more frequent than control in 1 litter and slightly more in 2 others. Three litters showed no incidence in any group.

Teratology: These examinations were done on a third litter of the F_3 generation. Sacrifices were done on the 21 day of gestation. No deleterious effects attributable to permethrin exposure were found in the following measures:

Pre-implantation loss
Post-implantation loss
Mean litter size
Mean litter weight
Sex ratio

The numbers of corpora lutea, implantations, and viable fetuses were all substantially increased at 250 ppm. A secondary consequence of the larger litter size was that the individual fetuses averaged a lower weight.

Soft tissue examination of about half the fetuses revealed neither treatment related nor unusual effects.

Skeletal examination of the remaining half of the fetuses revealed increases 14th ribs, wide fontanelles, and delayed vertebral ossification. However, the individuals showing these features were concentrate in few litters. The numbers of affected litters was not increased. There was no dose dependancy.

Category: Core guidelines

Conclusions: The NEL for permethrin effects on offspring of treated mothers cannot be determined from this study, but must be less than 500 ppm. At this dose, the offspring showed centrilolular hepatocyte hypertrophy and cytoplasmic eosinophilia, and buphthalmos with persistent pupillary membranes. Both of these effects showed dose dependancy. At 1000 and 2500 ppm parents had whole body tremors, while offspring showed them only at 2500 ppm.

Reproductive performance appeared only to be enhanced, as mothers fed 2500 ppm had more corpora lutea, implantations, live births, and larger litters with better survival.

RAT: Special Study of the Reversibility of Hepatic Biochemical and Ultra Structural Changes

The rats used were female SPF-Wistar derived animals 3 weeks old from the Alderley Park Colony. The Central Toxicology Labs of ICI-Ltd., England conducted the study.

It was submitted by ICI-Americas, Inc., Wilmington, Delaware on January 27, 1978, as report #CTL/P/354.

The dose of permethrin studied was 2500 ppm which was compared to control. Each group was composed of 12 animals. The four groups were fed the study diets for 4 weeks. One group was sacrificed immediately, and the others after 1, 4, and 8 weeks of recovery. The diets contained corn oil as a mixing vehicle and were pelleted.

Results:

Clinical Observations: One animal had tremors during the first week of permethrin.

Body weights: Weight gain was reduced by permethrin feeding. During recovery, the rate of gain matched controls, but the previously induced difference persisted.

Food utilization: Food consumption was reduced. (Spilled food was also collected and weighed for this calculation.) Food utilization was also reduced. These reverted to control levels during recovery.

Liver weights: Increased weights were found after 4 weeks of permethrin feeding. One week of recovery reduced the difference to $P = 0.1$. The liver to body weight ratios continued to show significant organ enlargement at each of the recovery sacrifices.

Biochemistry: SGPT was not altered in any group. Hepatic content of P-450 and activity of aminopyrine-N-demethylase were increased by permethrin feeding. The difference between treated and control was much less after 1 week of recovery. All values were in the normal range after 4 or 8 weeks of recovery. These measures were based on 8 rats per group.

Necropsy: No permethrin induced changes were found.

Electron Microscopy: Morphometric analysis of smooth endoplasmic reticulum showed proliferation after 4 weeks feeding of permethrin. One week of recovery reduced this difference. No differences remained after 4 or 8 weeks of recovery. These measures were based on 6 rats per group.

Category: Core-Minimum data

Conclusion: This study strongly supports the contention that permethrin is an inducer of the mixed function oxidose, cytochrome P-450 system, and that this induction is reversible. The return to control values for these activities took more than 1 week but less than 4 weeks after 4 weeks of feeding. However, as the liver to body weight ratios did not return to control values by 4 or 8 weeks after termination of feeding it is not clear that enzyme induction was the sole hepatic alteration.

RAT: Special 6 Month Study of Liver Hypertrophy

The rats used were 5 weeks old SPF-Wistar derived animals from the Alderley Park Colony. Central Toxicology Labs, Ltd, England conducted the study starting Febrary 15, 1977. It was submitted by ICI-Americas, Inc., Wilmington, Delaware on January 27, 1978 as study #CTL/P/360.

The doses of permethrin studied were 20, 100 and 1000 ppm, which were compared to controls. The permethrin was mixed in the diet in corn oil. The diet was then pelleted.

Each group contained 24 animals of each sex. Eight animals from each group were killed at the conclusion of 6 months of feeding. The others were killed at a later time, and no terminal data were submitted for any of them.

Results:

Clinical Observations: Stained tails were seen on males from week 16. C=4, 20 ppm = 6, 100 ppm = 13, and 1000 ppm = 8. In addition, ringtail was seen in all groups.

Mortality: One male fed 100 ppm was found dead week 25 with no obvious cause of death.

Body weight: Rates of gain among females fed 20 or 100 ppm were like control. Those fed 1000 ppm gained a statistically significant 6% less than control by week 20 but the difference in attained body weight was negligible.

Similarly, males fed 20 ppm showed no suppression of weight gain. Those fed 100 or 1000 ppm showed an immediate retardation of weight gain. By week 2 both groups averaged at least 7% below control weights. Again the attained body weights showed negligible difference from control.

Food consumption: Any differences between groups appeared to be sporadic. Food utilization was unaffected.

NOTE: For all of the remaining measures, only 8 animals per sex per dose were examined.

Liver weights: Liver weight and organ to body weight ratio showed increases at 1000 ppm, but none at 20 or 100 ppm.

Biochemistry: Hepatic animopyrine-N-demethylase activity was increased 70% in males fed 1000 ppm, and 25% in males fed 100 ppm. The latter was not significant unless a log transformation was used. Among females, the increases were 150% at 1000 ppm and 30% at 100 ppm; with similar significances. Those fed 20 ppm showed very little difference from control.

Content of cytochrome P-450 was increased only in males fed 1000 ppm--by 18%. All others were comparable to control.

Necropsy: No abnormalities were found which could be attributed to permethrin feeding.

Electron microscopy: Proliferation of smooth endoplasmic reticulum was measured. Increases were seen in males and females fed 1000 ppm. Among those fed 100 ppm. 4/8 males and 1/8 females showed proliferation. No alteration were seen in livers from rats fed 20 ppm. No other abnormalities were seen.

Category: Core-Minimum data

Conclusions: The NEL determinable from this study is 20 ppm. At 100 ppm there was a reduced early weight gain in males which was also seen at 1000 ppm. In addition, some animals at this dose appeared to have increased smooth endoplasmic reticulum, and had a barely significant increase in hepatic aminopyrine-N-demethylase. At 1000 ppm both these effects were much more pronounced, and males showed increased cytochrome P-450.

☑ RAT: 2-Year Feeding Study--Combined Toxicity/Oncogenicity

The rats used were SPF-Wistar derived animals, 4 to 5 weeks old and bred in the Alderley Park colony. The study was conducted at the central Toxicology Labs of ICI, Ltd., England, beginning in August 1975, as report #CTL/P/357.

The study was submitted by ICI-Americas, Inc., Wilmington, Delaware on January 29, 1978.

Doses of 500, 1000, and 2500 ppm were studied in addition to controls. Each group contained 60 males and 60 females. Twelve rats of each sex were designated for sacrifice at one year. The permethrin was mixed with corn oil before incorporation into a stock diet which was then pelleted.

Results:

Clinical Observations: All males and many females fed 2500 ppm permethrin had whole body tremor and piloerection during the first 3 weeks. During the first two weeks they were also hypersensitive to external stimuli. Neither controls, nor rats fed 500 or 1000 ppm had these signs. (1000 ppm initially yielded 140 mg/kg/day.)

Rats from all groups had stained fur about the tail or genital area. This appeared to be a dose dependant increase in duration and severity among both males and females. However, incidence increased only among males. The lowest lose, 500 ppm, caused substantially more staining than control.

Mortality: The percentage of animals which had died at various times is shown below:

	Males				Females			
ppm	C	500	1000	2500	C	500	1000	2500
Week 24	0	0	0	3.3	0	0	0	0
Week 52	3.3	0	1.7	8.3	1.7	0	0	0
Week 76	9.6	8.3	18.3	20.8	7.8	2.1	2.1	4.2
Week 104	47.5	41.7	42.6	58.3	36.5	29.2	25.0	22.9

Males fed 2500 ppm had excess deaths throughout. While no more males fed 1000 ppm died, than did controls, many of died substantially earlier.

Body weights: These were recorded weekly for the first 12 weeks and then biweekly. There were no important differences between any of the treated groups and control at anytime during the study.

Food Consumption: This was measured as the pooled value for 4 animals, or one cage of females and two cages of males. Measurements were recorded weekly for 12 weeks. Then up to week 32, measurements were made every 4th week. Finally, 3 consecutive weekly determinations were made about every 12 weeks.

Overall food consumption was remarkably uniform among all groups of each sex.

Hematology: Samples taken pretreatment, at 4 and 13 weeks and every 13 weeks throughout were analysed for HGB, PCV, WBC, differential (of 100 cells), platelet count, red cell morphology and MCHC. From week 52, RBC, MCH, and MCV were also determined. Samples were taken from a different 8 males and 8 females per group at each sample time.

No group mean difference of biological importance was found.

Coagulation: Prothrombin and activated partial thromboplastin times were measured on samples from 8 rats per sex per dose sacrificed at 1 or 2 years. Statistically significant but biologically slight prolongations were found at both 52 and 104 weeks, only in males. Both those fed 1000 ppm and those fed 2500 ppm had prolonged times. Longer times without statistical significancewere also shown by the data for males fed 500 ppm. The consistency, dose-dependancy, and repeatability of these changes suggests a relation to permethrin feeding, even though the sizes of the differences were only a few seconds.

Blood chemistries: Samples were taken on the same schedule as hematology, but from different animals. The same 8 males and 8 females were sampled repeatedly for blood chemistry measures. Analyses included SGPT, SGOT, urea, and glucose. There were individual animals with changes related to subsequently fatal pathology or neoplasia. There were none that could be attributed to treatment.

Liver enzymes: Hepatic aminopyrine-N- demethylase (APND) activity was increased at both 52 and 104 weeks with dose dependance. The tabulation shows percent increase over control from the means of 4 rats per sex per dose.

	Males			Females		
ppm	500	1000	25000	500	1000	2500
Week 52	82%	94%	248%	38%	267%	314%
Week 104	79%	135%	454%	30%	28%	214%

Urinalysis: Pooled samples were collected over 18 hr from 4 males and 4 females per group, prior to treatment and every 13 weeks. These were analysed for volume, protein, pH, specific, gravity, glucose and bilirubin. Volume seemed to increase by the end of the study from males and females fed 2500 ppm. Protein also appeared to increase, particularly weeks 91 and 102 in males fed 2500 ppm.

Microscopic examinations of sediment were done individual urines from 3 or 4 animals per sex per dose at 18, 21 and 24 months. Different numbers of cells of various types were recorded. Because of the scatter and small n biologically meaningful effects would be undetectable.

Ophthology: Eight animals per sex per dose were examined at 18 months. Survivors of these 8 animals were re-examined at 21 and 24 months. Those which died were replaced up to 6 at 21 months and 8 at 24 months.

How replaced?

One female fed 1000 ppm developed bilateral corneal opacities between 21 and 24 months. All changes in other animals were unilateral.

Bone Marrow: Smears were made from 8 males and 8 females per group at 1 year and 2 year sacrifices. One male fed 2500 ppm "had an increased myeloid: erythroid ratio." No other information and no data were provided.

Organ weights: For all animals sacrificed at 1 and 2 years, the weights of the following organs were recorded: heart, lung, kidney, gonads, spleen, liver, adrenal, pituitary and brain. Thymus glands were also weighed at 1 year.

Group means of nonneoplastic organs which were at least 10% different from control included liver, kidney, spleen, ovaries, pituitary, and adrenal.

Liver weights were increased among both males and females fed 2500 ppm for 1 year. After 2 years, liver weights and liver to body weight ratios were increased in males treated at all doses. Liver weights were then increased also in females fed 1000 ppm.

Kidney weights were increased with kidney to body weight ratios 14 to 25% above controls, among all groups of treated males.

Two year spleen and spleen to body weight ratios were decreased among males fed 500 or 2500 ppm.

Adrenal weights in males fed 500 ppm for 1 year were 20% heavier than control. The difference did not recur at 2 years.

Pituitary weights were increased among all groups of treated males at 1 year, but only in those fed 1000 or 2500 ppm at 2 years.

One year, but not 2 year, ovary weights were increased 22% among those fed 500 ppm but decreased 12% among those fed 1000 ppm.

Gross pathology: The usual variety of changes were reported. Four treated males, but no controls, bore skin growths which were not examined histologically, but resembled either papillomas or epidermoid cysts.

Histopathology: Nonneoplastic changes which showed some possible relation to permethrin feeding were few.

Calcification of the renal pelvic epithelium showed increased incidence, but not severity, in all groups of treated females.

Focal adenitis of the sublingual gland was found in 4 or 5 rats per sex at 1000 and 2500 ppm, and 2 or 3 at 500 ppm. Only one control, a male, showed this change.

Hepatocyte vacuolization was seen with increased incidence in all groups of treated males and with increased severity among both males and females fed 2500 ppm and females fed 1000 ppm. Hepatocyte hypertrophy also appeared to be chemically induced, with increased incidence in both sexes at 2500 ppm and males fed 1000 ppm. These were not necessarily linked, but appeared to be separate manifestation. While the hepatocyte hypertrophy was predominantly centrilobular, the vacuolization was commonly periportal, or scattered throughout.

Microbiology and Virology: Moderate respiratory distress was noted about week 70 in about one-fifth of the rats. Antibodies to Sendai and mouse pneumonia viruses were found at high titer. 95% of all animals tested at terminal sacrifice has antibodies to these viruses. None had Polyoma virus antibodies, one had antibodies to Reo III and 6 to 15% had antibodies to Minute, Toolan and Kilhan viruses. No interpretation of these findings was offered.

Neoplasia: The incidence of neoplasia in various groups follows:

	Males				Females			
ppm	C	500	1000	2500	C	500	1000	2500
rats dying spontaneously:								
# with neoplasms	15	15%	14**	18*	17	13	11	11
# examined	23	20	21	28	17	14	12	11
% incidence	65%	75%	67%	64%	100%	93%	92%	100%
rats sacrificed at 1 year:								
# with neoplasm	0	0	1	1	2	5	1	2
# examined	12	12	11	11	11	12	12	12
% incidence	0	0	9%	9%	18%	42%	8%	16%
rats sacrificed at 2 years:								
# with neoplasms	19	20	20	15	24	29	29	30
# examined	25	28	28	20	31	34	36	37
% incidence	76%	71%	71%	75%	77%	85%	81%	81%
Total								
# of distinct neoplasms	54	46	49	57	73	73	77	79
# rats with neoplasms	34	35	35	34	43	47	41	43
# of malignancies	9	6	9	12	9	10	8	10
# of neoplasm of types not seen among controls:								
malignancies	-	1	1	1	-	0	0	4
benign	-	6	6	3	-	8	5	4

** Ten of these animals, and *five of these died prior to the first control death with neoplasia.

Treated males dying with neoplasms died early. The first control male to die with a neoplasm died week 84. By that time 5 males from each of the groups fed 500 and 2500 ppm and 10 of those fed 1000 ppm had already died with neoplasms, 60% of which were malignant in each group. For males fed 1000 ppm this difference is statistically different at P = .002. No timing differences occurred among females.

Among the types of malignancies which occurred among treated but not controls, 3 mammary adenoacanthomata, and a keratoacanthoma, all at 2500 ppm are of interest because of their relation to squamous cell carcinomas. The squamous cell carcinomas which did occur in both treated

and control animals, developed in unusual sites among treat animals. Two were found in the corpus of the uterus in females fed 1000 ppm. The thymus was the site in one female from each treatment group, and in one male fed 2500 ppm. The tooth socket was the origin of one in another male fed 2500 ppm. The others were in skin. The totals including acanthomas, suggest a dose-dependancy. There was one in a control male, one in a 500 ppm female, five at 1000 ppm, (2 in males and 3 in females) and 8 at 2500 ppm (4 in each sex). The χ^2 test for controls versus 2500 ppm yields $0.05 > P > 0.02$.

Of the benign neoplasms which occurred only in treated animals, the most common were skin papillomas. There were 3 affected animals in each group of treated males. It is interesting that there are both benign and malignant neoplasms increased in treated groups which may involve proliferation of squamous cells with varying degrees of keratinization.

Benign mammary neoplasms were both more numerous and more varied among treated females. However, none of these differences achieve statistical significance.

ppm	C	500	1000	2500
# of animals with mammary neoplasms	10	10	11	17
# of mammary fibroadenomas	11	9	11	19
# of other mammary neoplasms (including papillomas, papillary adenoma, and adenoma)	10	2	3	3
	21	22	25	39

Category: Minimum data

Conclusions: Squamous cell carcinomata, including variously keratinized subtypes, appear to be increased by treatment with permethrin. The increase appears to be dose dependant. In addition, promoter activity is suggested for males, among which those fed 1000 ppm has statistical significant early deaths in the presence of neoplasia.

Aside from the apparent oncogenic effect noted above, a systemic NEL cannot be determined from this study, but must be lower than 500 ppm.

The liver is a target organ, showing several effects of feeding at all doses of permethrin among males, females, or both. Hepatic microsomal enzyme induction was demonstrated. Other observed effects which may or may not be benign manifestations of this included increased amounts of smooth endoplasmic reticulum, increased liver weight and liver to body weight ratio and centrilobular hepatocyte hypertrophy. However, non-regional hepatobyte vacuolization and slight, but dose dependant,

prolongation of prothrombin time and activated partial thromboplastin time, were seen, and are less likely to represent the enzyme induction.

All groups of treated males also showed increased weights and organ to body weight ratios of kidney and pituitary. All groups of treated females had induced calcification of the renal pelvic epithelium. Both males and females at all doses showed increased staining of the fur in the perigenital area and on the tail.

Other changes, identified as probably induced by permethrin feeding occurred only at 2500 ppm. During the first 3 weeks, both males and females exhibited whole body tremors, piloerection, and hyper reactivity to external stimuli. In the latter part of the study there was a slight excess mortality among males. Urine volume and protein concentration may also have been increased.

Parish 7

MOUSE: 90-Week-Lifetime Feeding/Chronic Toxicity/Oncogenicity

The mice used were Alderley Park strain from their own breeding colony. The study was conducted at the Central Toxicology Labs of ICI, Ltd., England, beginning in November 1975. It was submitted by ICI Americas, Inc., January 27, 1978 as reports CTL/P/358 and CTL/P/359.

Doses of 250, 1000, and 2500 ppm were studied in addition to controls. Each group started with 70 males and 70 females. Ten males and ten females were included in each of two interim sacrifices; done at 6 and 12 months. The permethrin was added to corn oil for mixing in the diet, which was then pelleted.

Results:

Clinical Observations: The submission stated only the following:

"The general health and condition of the animals remained good throughout the study. The few clinical abnormalities seen were distributed across all groups and there was no evidence of any change due to PP557."

Mortalities: There was a slightly increased mortality at 2500 ppm in both sexes.

Body weight: No biologically significant differences occurred.

Food consumption: All of the treated groups ate about 10% more than controls during weeks 9 through 11 or 12. There was no evidence of a dose relationship. At other times the only apparent differences had no pattern and tended to balance out.

Hematology: Samples were taken at the 6 and 12 month sacrifices. There was a statistically significant 22% increase in platelets among males fed 2500 ppm for 6 months. The individual values were not extreme, but clustered about the upper part of the normal range. As there was no evidence of progression at 1 year this cannot be considered a biological abnormality. Other parameters showed no differences. These included HGB, HCT, MCHC, WBC, differential (of 100 cells), and red cell appearance.

Bone Marrow: Smears made from 5-6 mice per sex per dose at the 1 year sacrifice showed no abnormalities.

Blood Chemistries: Usable samples were obtained from 5-10 mice per sex per dose at 6 an 12 month sacrifices. No biologically important differences were found in SGOT, SGPT, BUN, and glucose.

Liver enzyme: Aminopyrine-N-demethylase activity was measured in liver samples from 3-5 mice per sex per dose at 6 and 12 month sacrifices. Males fed 1000 and 2500 ppm for 6 month showed activity which was 2-fold and 3.5-fold that of control, respectively. At 1 year, all groups of treated males had activities which were still higher than at 6 months, and higher than the 1 year control. However, the male controls showed more than a 3 fold increase over the 6 month activities. The impression is that all males were exposed to an extraneous microsomal enzyme inducer prior to the 1 year sacrifice. The females showed relatively low and uniform values at both times, although the 6 month levels were greater than those a 1 year.

Liver electron microscopy: Some of the same livers that were assayed for enzyme activity were also examined with the electron microscope. An occassional female showed some increase in smooth endoplasmic reticulum (SER) which was not consistent with enzyme activity. Among males all groups had individuals with abundant SER. The impression that all males were exposed to an extraneous hepatoactive material is further strenthened by the finding of multiple hepatocyte abnormalities which were similar across all treatment groups. These findings included cytoplasmic myelin

whorls, increased numbers of microbodies, lysosomes, nucleoli, and nuclear alterations.

Therefore, any conclusion regarding the activity of permethrin as an enzyme inducer after 1 year of feeding in male mice is unwarranted.

Urinalysis: Pooled samples were taken at 6 and 12 months. There were no trends in volume, pH, specific gravity, protein, glucose, or bilirubin.

Organ weights: Organs were weighed from 2 to 5 mice per sex per dose of those sacrificed at 6 or 12 month. At 98 weeks, organs were weighed from 7 to 11 mice per sex per dose.

Many organs were abnormally large due to the presence of neoplasms. Several spleens were enlarged, and showed marked extramedullary hematopoesis. Excluding these effect, there were statistically significant differences in the weights, and organ to body weight ratios, of liver, heart, and lung.

Liver showed the most reproducible changes. The table shows the percent change from control, for groups with a difference yielding $P < .05$.

	Males			Females		
ppm	250	1000	2500	250	1000	2500
6 mo. liver wt	N.S.	+17%	+37%	N.S.	N.S.	+32%
6 mo liver:body wt	N.S.	N.S.	+36%	N.S.	N.S.	+34%
12 mo liver wt	N.S.	N.S.	+48%	N.S.	+29%	+28%
12 mo liver:body wt	N.S.	+20%	+57%	N.S.	+27%	+34%
23 mo liver wt	N.S.	N.S.	+29%	N.S.	N.S.	+38%
23 mo liver:body wt	+27%	+37%	+68%	N.S.	N.S.	+47%

There was a high incidence of hepatic neoplasia among the male control mice selected from the terminal sacrifice for organ weight determinations. Only 2 were without neoplasms. In order, to establish a more adequate estimate of the normal range for liver to body weight ratio, it was tested whether this was the same for untreated males sacrificed at 6, 12, and 23 months of age. As there were no statistical differences, these were pooled. By use of this expanded control group, there was no longer any statistical evidence for abnormality among males fed 250 ppm for 23 months. A similar maneuver for females suggested no real effect following feeding

of 1000 ppm for 1 year. Although uniform chemical effects did not produce significant differences at low dose, it is apparent that some lower dose individuals are showing the same effect as higher dose animals. The percent of individual mice with liver to body weight ratios greater than any control from any sacrifice time shows a dose response curve. For males this is, 13% at 250 ppm, 47% at 1000 ppm and 100% at 2500 ppm. Females showed a slightly less steep dose-response curve, 16% at 2500 ppm, 35% at 1000 ppm, and 71% at 2500 ppm.

Heart weights were increased among females, only at 98 week sacrifice. Those fed 250 ppm and 2500 ppm had mean increases 16 to 30% both in organ weight, and organ to body weight ratio. The histopathology contained no suggestion of what portion of the heart was hypertrophied and had little abnormalities--even one heart which was 88% heavier than control.

Brains were increased 11% only among females fed 2500 ppm for 98 weeks.

Gross pathology: The usual assortment of changes associated with neoplasia and aging were found with no notable clustering in any group. There was excellent follow-up of such findings during the histopathology examinations.

Neoplasia: The incidence of neoplasia in various groups follows: The total number of animals per group is 70%.

	Males				Females			
	C	250	1000	2500	C	250	1000	2500
Mice dying spontaneously								
# with neoplasms	13	17	17	19	31	31	28	25
# examined	40	40	38	44	40	42	40	44
% incidence	33%	43%	45%	43%	78%	74%	70%	57%
Mice sacrificed @ 6 mo								
# with neoplasms	0	0	0	1	0	1	0	0
# examined	9	9	10	6	9	10	10	9
Mice sacrificed @ 12mo								
# with neoplasms	1	3	2	2	1	2	1	0
# examined	9	7	8	10	9	9	7	10
Mice sacrificed @ 23.mo								
# with neoplasms	11	7	8	7	12	8	9	7
# examined	12	14	14	10	12	9	13	7
TOTAL neoplasms	40	41	38	41	75	62	60	51

The most numerous neoplasms in both sexes were lymphomas and lung neoplasms. Among females there were also many pituitary adenomas. Males showed several neoplastic liver nodules. This strain of mice has been reported to have a very high and eractic spontaneous incidence of these tumors. Although the neoplastic liver nodules appeared in the 12 month sacrifices in two males from each dose group. In addition, one male fed 2500 ppm and sacrificed at 6 months also bore similar nodule. Males fed 2500 ppm also died early with these nodules. The numbers discovered among treated males prior to finding one in a control male were 3 at 250 ppm, 2 at 1000 ppm and 7 at 2500 ppm. The total numbers of type A neoplastic nodules were 10 in control 7 in each of the groups fed 250 and 1000 ppm, and 14 in those fed 2500 ppm.

The sponsor identified lung neoplasms as being increased by use of a log rank method, but not by use of the Fisher's Exact Probability Test. The numbers were distributed as follows:

	Males				Females			
ppm	C	250	1000	2500	C	250	1000	2500
lung adenoma	10	6	12	17	11	8	10	15
adenocarcinoma	0	0	0	0	0	1	1	1

These do not appear to constitute an oncogenic potential. The incidence of other types of spontaneous neoplasm showed even less suggestion of a chemical dependant effect. Neither were there any notable pattern of neoplasms of types which occurred in treated but not control animals.

Histopathology: Vacuolization of the renal tubular epithelium was substantially less pronounced among males fed 2500 ppm than others at all 3 scheduled sacrifices.

Hepatocytes showed cytoplasmic eosinophilia which was related to both dose and duration of feeding. At 6 month sacrifice only those fed 2500 ppm showed it. Among males, the incidence was 2 of 6 and in females, 6 of 9. By one year, not only those fed 2500 ppm, but also 2 of 9 females fed 1000 ppm exhibited this change. At 23 months, both sexes and both those fed 1000 ppm and 2500 ppm showed the effect. At high dose, between 50 and 70% of the animals sacrificed at 12 or 23 months were affected. Neither controls, nor those fed 250 ppm showed this change.

No other changes appeared to be related to feeding of permethrin.

Category: Minimum Data - Oncogenicity. Bone, nasal cavities and middle ear were not sectioned. Neoplasms were not weighed. This strain of mice also has a substantial and erratic spontaneous incidence of neoplasia.

Supplementary - Chronic Feeding. The study was very carefully executed. However, the protocol did not provide a sufficient spectrum nor frequency of clinical determinations, nor numbers of mice.

Conclusions: A systemic NEL is not determinable from this study, but must be less than 250 ppm. At that dose, females sacrificed at 98 weeks had increased heart weight and heart to body weight ratios. These were also seen among females fed 2500 ppm. Both sexes showed some liver changes at various times at both 1000 and 2500 ppm. These included increased liver weight, increased liver to body weight ratio, induction of microsomal enzyme activity, electron microscope evidence of increased smooth endoplasmic reticulum, and hepatocyte eosinophilia.

Changes seen only at 2500 ppm were few. Males showed absence or substantial reduction of the normal vacuolization of the renal tubular epithelium. Females showed increased brain weight, and brain to body weight ratio.

Potential exposure analysis: Aside from the apparent oncogenic effects (discussed for the 2-year rat study above, and in the 2 oncogenicity studies reviewed in the memo of 3/30/78, an NEL of 20 ppm is confirmed for the rat.

An ADI of 0.01 mg/kg bw/day can be calculated, using a 100-fold safety factor. This is equivalent to 0.6 mg/day for a 60 kg man.

The maximal theoritical exposure would be composed of the following:

at 0.5 ppm -	cotton seed oil (as all vegetable oil)	yields	0.0015 mg/day
at 0.05 ppm -	meat (including cattle, hogs, horses, goats, sheep, and poultry.)	yields	0.0137 mg/day
	milk	yields	0.0284 mg/day
	eggs	yields	0.0027 mg/day
TOTAL			0.0463 mg/day

Comments: (1) The petitioner contends that hepatic hypertrophy is merely a manifestation of microsomal enzyme induction, and should not be considered as an effect for the purposes of determining on NEL. This reviewer disagrees.

Data from several studies support the conclusion that permethrin simultaneously increases aminopyrine-N-demethylase activity, cytochrome P-450 and smooth endoplasmic reticulum contents, and liver weight. However, in the only study of the reversibility of these changes, each parameter returned to control levels, except liver size. This calls into question the assumption that microsomal enzyme induction is the sole change involving liver enlargement. Therefore, such enlargement cannot be neglected.

(2) The mouse study reviewed previously (memo of 3/30/78) showed statistically significant increases in incidence of lymphomas among females fed 20 or 500 ppm. Those fed 4000 ppm showed no increase. One mechanism of neoplasia for high incidences at low doses and low incidences at high doses pertains to chemicals which induce hepatic microsomal enzymes. Such results are found when the parent compound is an oncogen, but its metabolites are not, and the oncogenic dose is below the enzyme inducing dose.

The data for the mouse lymphomas is consistent with this view. Those fed 4000 ppm had increased liver weight and liver to body weight ratios. The lower dose females did not have livers which differed from control weight.

In order to distinguish an oncogenic potential from a false positive result, it would be desirable to have a second mouse study using "sub-inducing" doses. The current review would appear to contain such a study. The lowest dose was 250 ppm which is between the doses which were positive in the first study. In addition, for those fed 250 ppm, liver weights never differed from control, including measurements taken at 6 and 12 month interim sacrifices. However, there are reservations about the applicability of the mouse strain used (ICI mice) in the second study based on published data. An article entitled, "The predictive value of carcinogenic tests in ICI-mice, " by B.J. Leonard of ICI-Alderley Park, appeared in 5th ICLA Symposium, Gustar Fisher Verlag, Stuttgart, 1973 pp 249-267. This lists the incidence of several neoplasms in 19 control groups of ICI-mice. The number of animals per test varied from

41 to 525. The incidence of (spontaneous) lymphomas varied from 1.7% to 58.5%. About half of the studies showed an incidence of 25% or greater. This makes it difficult to accept a study using these mice as an applicable negative replicate.

R/D Init: REngler 1/14/78
MP/ccw

10/4/78

END